State of the Art in Malignant Melanoma Therapy: Bench to Bedside

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Disclosures
Ad Boards: OncoSec, NeoStem, Nektar, Prothena

The presentation will discuss but not endorse the use of investigational agents and the possible use of drugs for as yet unapproved indications

Topics to cover—immuno

Bench	Bedside
Interferons	Adjuvant>>advanced
Interleukin-2	Proof of principal but poor therapeutic index
CTLA4 blockade	Checkpoint blockers augment existing immune response
PD-1, PD-L1 blockade	TIL cells exploit immune tumor microenvironmet
Tumor-infiltrating lymphocyte regimens	Potent locoregional responses→systemic benefit
Lesional, local approaches	

Topics to cover—molecular

Bench	Bedside
Discovery of BRAF activating mutation in melanoma	Rapid and dramatic responses to specific BRAF inhibitors
Other oncogenic drivers, some in other tumors	Equally dramatic emergence of resistance, sometimes mixed
Rapid emergence of resistance uncovered multiple new targets	Therapeutic index and drug interactions may limit combinations (like early ART)
Combinatiosn appear promising therapeutically	

Interferons—type I and II

Bench	Bedside
IFN-α has pleiotropic immunomodulatory effects	Widespread use in adjuvant Rx at high doses/long durations
Modest activity vs advanced melanoma but optimal with ↓ tumor burden	Controversy remains re: risk and cost:benefit ratios
Poorly-"customized" re: predictors of benefit/failure/tox	
IFN-γ—narrower, different immunomodulatory effects but hard to harness therapeutically	IFNs likely to be supplanted by narrower-activity cytokines in cancer

Interleukin-2

Bench	Bedside
Murine data showed benefit dependent on dose, elaboration of LAK cells	High doses required for clinical benefit=5-7% durable remission
Receptors related to other γc cytokines	Multi-organ toxicities life-threatening, limit access to selected pts, Rx centers
Toxicities mediated by capillary leak, other cytokines	Predictive factors may be based on host, tumor factors (CWG "select")
Mechanisms poorly-understood: increased AICD, Treg undesirable	Altered versions, enhancements and toxicity protectors all failed
	Lower doses → T cell survival in adoptive T cell Rx

CTLA4 blockade

Bench

- CTLA4 competitively inhibits CD28:B7.1 binding after T cell activation
- Embryonic -/- causes lethal lymphoproliferative syndrome
- Ab to CTLA4
  - Removes the inhibitory signal
  - Depletes Treg cells
  - Enhances melanoma-specific T cell motility

Bedside

- Fully-human CTLA4 Ab active in melanoma, sometimes with delayed response
- Autoimmunity in up to 30%
  - Colon
  - Skin
  - Pituitary
  - Liver
  - Others rarely
- Approved for advanced mel, RFS benefit in adjuvant mel

PD-1 axis blockade

Bench

- PD-1 mediates T cell exhaustion in viral, tumor immune responses
- Ligands—PD-L1, PD-L2
- PD-1 -/- phenotype→ autoimmune, not lymphoproliferative
- Blockade on either side reverses exhaustion

Bedside

- Phase I studies showed early, marked regression in 30-40% of patients
- Several human or humanized Abs studied, 2 approved 2014
  - Nivolumab in Japan
  - Pembrolizumab in U.S. (accelerated, 2nd/3rd line)
- Ph IIIs test benefit of PD-1 and/or combined PD-1/CTLA4 block
- Will PD-1 or PD-L1 block or combination with ipi "win"?

Other immunotherapy combinations

Bench (or early trials)

- Inhibitors of negative regulators in tumor microenvironment
  - IDO inhibitor of MDSC
  - PLX3397 inhibitor of RTKs in tumor macrophages
- Immune costimulation
  - 4-1BB-Ab, CD40L, OX40-Ab
  - GM-CSF with ipilimumab
- Vaccines?

Bedside (later trials)

- CTLA4 +/- bevacizumab
- Other γc cytokines, e.g. IL15 + PD-1 blk
- CTLA-4 Ab plus radiotherapy
- Enhancers of ADCC
- Lesional, regional delivery
  - Viral→ imm'mod genes
  - Cytokines, DC activators

Tumor-infiltrating Lymphocytes

Bench

- Adoptive/autologous immune cell Rx melanoma>>others
  - Lymphodepletion required
  - T cell expansion and survival are critical
  - Exploration of antigens→ individual tumor mutations
  - ?Role of tumor manipulations
    - Systemic Rx incl targeted
    - Radiotherapy to tumor
- ?Other predictors "necessary and sufficient" for curative outcomes

Bedside

- Requirements daunting
  - Tumor accessible
  - Yield of TIL culture
  - ?tumor-specificity
  - Pt who can tolerate lymphodepletion, HDIL-2
- Outcomes encouraging in pts who get all components
  - ORR in 60-70% range
  - CRR in 15-20% range
  - PFS plateau?

Molecularly-targeted Rx

Bench

- BRAF activating mutations in >50% melanoma
  - Single site in 80%
  - Ras-independent activation
  - Transforming*
- N-Ras mutations (several sites) in 15-20%, nearly always exclusive of BRAF mut
- Other drivers include CDK, NF1, c-kit, GNA, fusion genes

Bedside

- First generation of inhibitors "dirty"→occasional response
- Early trials in unselected pts failed to improve cytotoxic Rx
- BRAF assays came with selective BRAF inhibitors
  - Dramatic responses if mut+
  - Rapid emergence of resistance

Resistance to targeted Rx

Bench

- Vertical (add MEK inhibitor) and horizontal (inhibit AKT/PI3K path) promising
- Rapid discovery of multiple resistance mech's→new drug targets, heterogeneity
  - CDK 4/6
  - Met
- Metabolic shifts, feedback loops and altered addictions

Bedside

- MEK inhibitors highly active as single agents in BRAF, not NRAS mutant
- Combined BRAF+MEK inhibition adds benefit
- Horizontal blockade strategies under investigation
- Therapeutic index likely to become unfavorable

Combination immuno+targeted

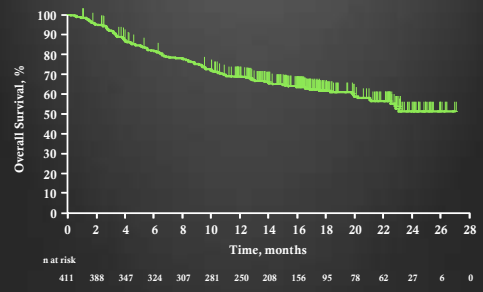
Bench

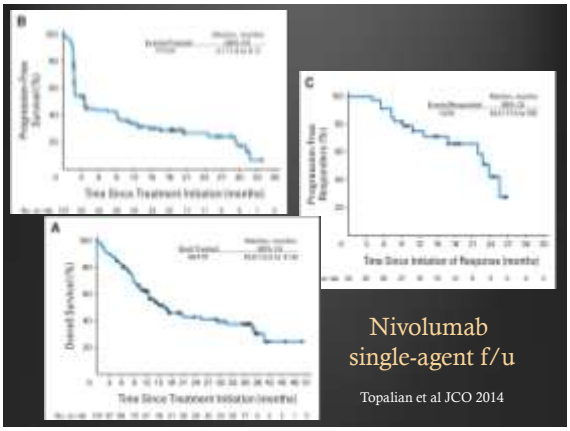
- BRAF inhibition enhances immune functions to control melanoma
  - T cell activity
  - MHC expression
  - PD-L1 ??
- MEK inhibition inhibits T cells—the drugs are not mutation/activation-specific because MEK is upstream-activated

Bedside

- Ipilimumab plus vemurafenib caused hepatotoxicity
- PD-1 blockade plus targeted agents may be more tolerable

Pembrolizumab single agent data in advanced melanoma (Ribas et al ASCO 2014)

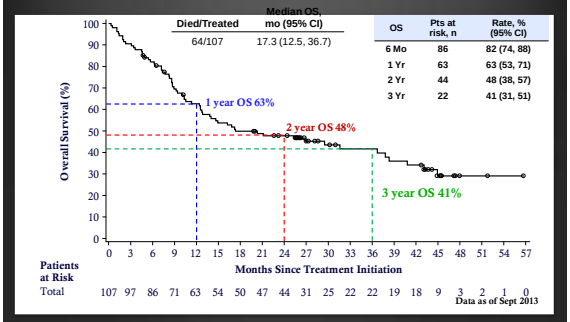




Nivolumab single-agent f/u

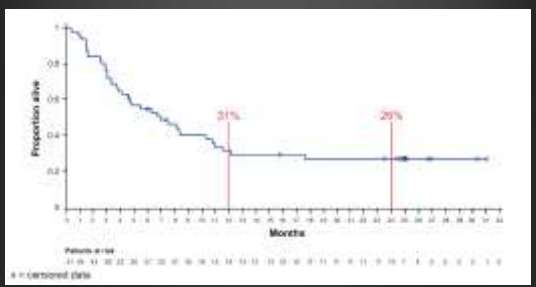
Topalian et al JCO 2014

Survival for adv melanoma on nivolumab



Presented by: F. Stephen Hodi, MD

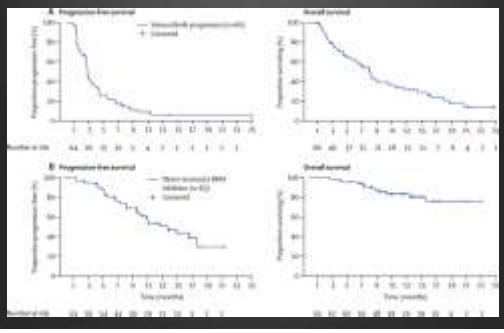
Survival of melanoma pts with brain mets Rx'd with ipilimumab



Heller ASCO 2011 after Margolin Lancet O 2011

Vemurafenib + cobimetinib

(Ribas et al Lancet O, 2014)



The world is moving fast!

Melanoma